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International application number: PCT/US05/008634

International filing date: 16 March 2005 (16.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/649,021
Filing date: 31 January 2005 (31.01.2005)

Date of receipt at the International Bureau: 20 April 2005 (20.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
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APPLICATION NUMBER: 60/649,021

FILING DATE: *January 31, 2005*

RELATED PCT APPLICATION NUMBER: *PCT/US05/08634*



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013105

22763 U.S. PTO

PTO/SB/16 (12-04)

Approved for use through 07/31/2006. OMB 0651-0032

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 276063275 US

112900 U.S. PTO
607649021

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Additional inventors are being named on the _____ separately numbered sheets attached hereto		
TITLE OF THE INVENTION (500 characters max):		
A METHOD TO USE TAT-BASED MOLECULES TO SUPPRESS REJECTION AND FACILITATE ESTABLISHMENT OF TRANSPLANTED STEM CELLS AND STEM CELL LINES		
Direct all correspondence to: CORRESPONDENCE ADDRESS		
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ENCLOSED APPLICATION PARTS (check all that apply)		
<input checked="" type="checkbox"/> Application Data Sheet. See 37 CFR 1.76		
<input type="checkbox"/> CD(s), Number of CDs _____		
<input checked="" type="checkbox"/> Specification Number of Pages 3		
<input type="checkbox"/> Other (specify) _____		
<input type="checkbox"/> Drawing(s) Number of Sheets _____		
Application Size Fee: If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).		
METHOD OF PAYMENT OF FILING FEES AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT		
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.		TOTAL FEE AMOUNT (\$)
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SIGNATURE

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Date

1/31/05

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(if appropriate)

Docket Number: 51311-00007

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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A METHOD TO USE TAT-BASED MOLECULES TO SUPPRESS REJECTION AND FACILITATE ESTABLISHMENT OF TRANSPLANTED STEM CELLS AND STEM CELL LINES

BACKGROUND OF THE INVENTION

[0001] Stem cell therapy is becoming established in the US and world-wide as a multi-billion dollar R & D industry. To achieve therapeutic efficacy and markets, stem cell programs must overcome several obstacles, including: 1) isolation of enough stem cells to be effective after transplantation; 2) delivery of an active stem cell population to the target organ; and 3) maintenance of viable stem cell transplants over time.

[0002] Significant progress is being made in the first two areas. Adult stem cells can now be freshly isolated from bone marrow, while immature stem cells can be freshly isolated from neonates or the teeth of youngsters. Stem cells have also been established in culture as long term cell lines for possible re-introduction into diseased individuals. They can be delivered intravenously, after which they hone to various organs including the heart where they may dramatically improve ejection fractions in individuals with chronic congestive heart failure (CHF).

[0003] Maintenance of stem cells after transplantation has not been adequately addressed, and importantly the magnitude of this problem is becoming increasingly apparent. On January 23, 2005 in the prestigious journal *Nature Medicine*, Varki and colleagues reported on-line that foreign cell-surface sialic acid molecules contaminate all currently available human stem cell lines. Since similar glycosylations contaminating pig xenografts result in acute graft rejection even if the grafts are fully compatible at all major histocompatibility (MHC) loci, it is very likely that these foreign glycosylations will induce rejection unless tolerance can be induced. Current standards of immunosuppression are generally ineffective at reversing acute allograft rejection.

[0004] One potential method for overcoming this obstacle would be re-introducing fresh stem cells isolated from the diseased individual or from a matched donor, likely a relative. These methods have problems, particularly for individuals over sixty who are the most immediate market for many therapies, such as those for CHF. Stem cells

isolated from older individuals are dramatic-ally reduced in number and potency, meaning that MHC-matched donors are a more realistic source. However, renal allografts are not currently recommended in the US for recipients over sixty even if perfectly MHC-matched donors can be found, because current immunosuppressives fail to tolerize for the donor organ likely because it contains other mismatches.

DETAILED DESCRIPTION OF THE INVENTION

[0005] We have reported elsewhere a method for producing biologically active Tat (a molecule from the Human Immunodeficiency Virus) that induces antigen-specific tolerance (PrecisionTolerogens™ (PT))when administered to animals along with co-antigen. This method works by inducing a class of suppressor macrophages overexpressing Fas ligand (see Cohen issued patent #6,667,151 which is incorporated herein in its entirety) and other immunosuppressive molecules including interleukin 10. Strategies using adenovirus vectors to induce Fas ligand over-expression in macrophages have been reported to tolerize animals against a wide variety of antigens normally associated with acute allograft or xenograft rejection (see Mountz *et al*).

[0006] We will engineer PT™ to produce antigen-specific tolerance to foreign molecules in stem cell transplants, be they derived from fresh donors or from cell lines. In cases where these antigens are defined, such as the sialic acid linkage Neu5 Gc (Varki), the determinant can be physically linked to the PT and administered IV or sc to the patient prior to transplantation. When alloantigens are not fully defined, a class of immunosuppressive macrophages will be generated *ex vivo* by coculturing patient's monocytes with PT and donor stem cells as a source of alloantigens. 72 hours later (at a time when the macrophages first become suppressive) the transplant containing donor stem cells and PT will be administered intravenously into the patient.

I claim:

1. A method for preventing graft rejection comprising linking Tat to a defined alloantigen in a stem cell transplant, such as Neu5GC, and thereafter administering the Tat-alloantigen complex directly to a patient.

2. A method for preventing graft rejection comprising co-culturing Tat-alloantigen complex with recipient monocytes *ex vivo* in the presence of donor stem cells for a sufficient period of time (48 hours-6 days) to induce a fully tolerogenic state, and thereafter introducing the Tat-alloantigen complex along with donor stem cells into the patient.

3. The method for preventing graft rejection according to claim 2 wherein several cycles of pretreatment with *ex vivo* generated Tat-alloantigen complexes are administered followed by one or several cycles of stem cell transplantation.

Application Data Sheet

Application Information

Application Type::	Provisional
Subject Matter::	Utility
CD-ROM or CD-R?::	None
Title::	A Method to Use Tat-based Molecules to Suppress Rejection and Facilitate Establishment of Transplanted Stem Cells and Stem Cell Lines
Attorney Docket Number::	51311-00007
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	0
Small Entity::	Yes
Secrecy Order in Parent Appl.?::	No

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